What % of patients with uncomplicated cystitis go on to develop pyelonephritis?

BOTTOMLINE

- Based on a meta-analysis of RCTs (N=2, n=962), there was no significant difference in risk of pyelonephritis among patients with treated or untreated uncomplicated cystitis (OR 0.33, 95% CI 0.04-2.70).
  - **Treated cystitis**: in patients who received an ABX pivmecillinam, or nitrofurantoin x 3 days, 0-0.15% of patients developed pyelonephritis.
  - **Untreated cystitis**: in patients who did not receive an ABX, 0.4-2.6% of patients developed pyelonephritis.
- Observational studies are lacking.
- Based on the limited available evidence with antibiotic regimens that are not recommended, 0 to 15 patients out of 10,000 who receive an antibiotic for uncomplicated cystitis may develop pyelonephritis. Empiric therapy with a narrow spectrum antibiotic is usually recommended for uncomplicated cystitis (e.g. nitrofurantoin x 5 days, TMP-SMX x 3 days). If the patient does not improve or worsens after 48 hours of antibiotic treatment, reassess the patient. If no pre-treatment culture available, culture patient. If pre-treatment culture available, tailor antibiotic to C&S. Also evaluate patient for pyelonephritis and other infections (e.g., sexually transmitted diseases).

BACKGROUND[1-11]

Uncomplicated cystitis includes premenopausal, non-pregnant♀ with no known urological abnormalities or comorbidities.
- Some experts also consider cystitis in postmenopausal or well-controlled diabetic ♀ to be uncomplicated.[1,3]

Uncomplicated cystitis incidence: 0.5-0.7/person-years in 18-40 year old sexually active ♀.[7]
- Cystitis is much more common than pyelonephritis (ratio of episodes of pyelonephritis to cystitis is 1:18-28).[8,9]

Pathophysiology: bacteria most commonly invade the urinary tract via the ascending route (urethra to bladder and in pyelonephritis bacteria continues to ascend up the ureter to the kidney).

Uncomplicated cystitis is generally considered a non-serious or benign infection from the perspective of long-term outcomes; however, there is some concern that pyelonephritis may be a complication of untreated cystitis.

For example, IDSA[2010] guidelines recommend antimicrobial treatment for all acute uncomplicated cystitis episodes as placebo therapy is associated with prolongation of symptoms as well as a small risk of progression to pyelonephritis.
- Note: all 1st line antibiotics for the treatment of uncomplicated cystitis are rated A-I.(strong recommendation based on high quality evidence)

Interestingly, some review articles question whether untreated cystitis progresses to pyelonephritis (and if so how often) due to the paucity of data;[5] and the occurrence of pyelonephritis episodes in the absence of cystitis symptoms.[11]

LITERATURE REVIEW[13-19]

Falagas et al. meta-analysis of RCTS (N=5, n=1144) of in non-pregnant ♀ with acute uncomplicated cystitis
- Risk of pyelonephritis (trials reporting pyelonephritis are summarized below)
  - antibiotic vs placebo (N=2, n=962): 0-0.15% vs 0.44-2.6%; OR 0.33 (95% CI 0.04-2.70)

Trials	Design	N	Inclusion Criteria	Exclusion Criteria	Intervention & Comparator	Pyelonephritis	Jadad Score*
Ferry et al.	MC, DB, RCT, f/u up 5-7 weeks, Sweden, 1995-97	884	non-pregnant, ≥18yr ♀ with uncomplicated UTI (dysuria, urgency, suprapubic or loin pain & bacteriuria [≥ 10^{3-5}cfu/mL])	genital infection, urinary tract abnormalities, DM, urinary incontinence, ≥ 1 sx of pyelonephritis (T≥38.5°, CRP ≥25, kidney tenderness)	pivmecillinam200-400 mg B-TID PO x3-7day vs placebo	1 case (0.15%, reason why not reported) vs 1 case (0.44%) (day of diagnosis not reported)	3
Christiaens et al.	MC, DB, RCT, f/u 2 weeks, Belgium, 1995-96	78	non-pregnant, 15-54yr ♀ with uncomplicated UTI (dysuria, frequency/ urgency & pyuria OR symptoms, pyuria,& bacteriuria [10^5cfu/mL])	gynecological sx, nephrological/ neurological abnormalities, DM, immune-compromised, recurrent UTI, T>39°	nitrofurantoin 100 mg QID PO x3 day vs placebo	0 cases (0%) vs 1 case (2.6%, diagnosed day 3)	3

*Comments: Systematic Review: 2/5 trials reported pyelonephritis complication rate, heterogeneity for this pooled estimate was not reported; AMSTAR 6/11 (see appendix); Individual RCTs: Jadad score 3/5 (≥3 considered adequate methodological quality[15,16]), small sample size, low pyelonephritis event rate, pyelonephritis only defined in Ferry et al. (elevated temp, CRP, kidney tenderness by palpation), pivmecillinam not available[CAN], nitrofurantoin 3 d course not recommended by IDSA (superior to placebo, but inferior to TMP/SMX for bacterial eradication; nitrofurantoin 5-7 d course considered standard of care).

Minimal observational studies available which include untreated, uncomplicated cystitis patients to characterize the natural course of the infection (likely because treatment was been considered standard of care prior industry requirements of robust study methodology [e.g., nitrofurantoin approved in 1953 by the FDA]). For example:
- **Little et al.** descriptive study (no control arm); N=684 non-pregnant ♀ with suspected UTI; ~7% did not receive an antibiotic (reasons for this were not reported) and pyelonephritis complications were not assessed/reported.

ABX antibiotic **BID** twice daily **C&S** culture & sensitivity **DB** double blind **DM** diabetes mellitus **FDA** Food & Drug Administration **f/u** follow up **MC** multi-center **OR** odds ratio **PO** oral **QID** four times daily **sx** symptoms **RCT** randomized controlled trial **T** temperature **TID** three times daily **UTI** urinary tract infection

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Appendix 1: AMSTAR Checklist (for systematic reviews ± meta-analysis)

AMSTAR Checklist	Falagas et al.
1. 'A priori' design?	N
2. Duplicate study selection & data extraction?	Y
3. Comprehensive literature search preformed?	Y
4. Status of publication (grey literature) used as an inclusion criterion?	N
5. List of studies provided?	N
6. Characteristics of included studies provided?	Y
7. Scientific quality of included studies assessed?	Y
8. Scientific quality of included studied used appropriately in formulation conclusions?	Y
9. Methods used to combine findings appropriate?	Y
10. Likelihood of publication bias assessed?	N
11. Conflict of interest included?	N
Total (/11)	6